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Orthogonality in Main Group Compounds: Direct One-step Synthesis of Air- and Moisture-stable Cyclophosphazanes by Mechanochemistry

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Mechanochemistry has been established to be an environmentally-friendly way of conducting reactions in a solvent-free manner. The development of mechanochemical orthogonal reactions, in which multiple reagents are milled together, can be a powerful strategy to selective yield the desired product. Such orthogonal synthesis, are rare, especially involving main group frameworks – based on bonds other than carbon – have yet to be reported. Herein, we demonstrate the direct formation of air- and moisture-stable cyclophosph(V)azanes enabled by an orthogonal "one-step one-pot" mechanochemical reaction. In addition, detailed hydrolytic- and air-stability studies, conducted over one and 12 months, respectively, revealed high robustness of these compounds.

In the last decade, the use of mechanochemistry as an alternative greener methodology to traditional solution-based methods, is rapidly gaining popularity amongst main stream synthetic chemists.[1-6] Amidst its obvious advantage as a solvent-free, environmentally-friendly synthetic technique, mechanochemistry has shown to significantly reduce reaction times and can enable the formation of compounds that were previously inaccessible when using conventional solution means.[5] The benefits of mechanochemical synthesis in the context of main group chemistry remains mainly unexplored.[7,8]

On the other hand, orthogonality in reactions can be employed as a strategy to truncate reaction steps, and enable efficient formation of desired products in a "one-pot" manner.[9] Orthogonality is often used interchangeably with chemoselectivity, and can be commonly described as two or more mutually exclusive reactions that can occur by different mechanisms.[9] However, to date, reports on orthogonal reactions in synthetic chemistry to achieve selective products are rare and far between.[10] In the case of main group compounds, the only reported orthogonal synthesis comprised a one-pot multi-step formation of indium complexes;[11] however, multi-step orthogonal methodologies involving main group frameworks – based on bonds other than carbon – have not been explored at all.

Recently, we have demonstrated the first mechanochemical solvent-free strategy for the synthesis of cyclic and acyclic phosph(III)azane frameworks.[6] Cyclophosph(III)azanes – $[XP(\mu\text{-}NR)]_2$ (R = alkyl or aryl and X = halogen, alkoxy, aryloxy or amino) – are a rich family within the main group chemistry arena[12-14] that have been used as ligands in coordination chemistry;[12,15-17] as building blocks for macromolecules,[18] larger inorganic frameworks and coordination polymers,[12,19,20] as well as, in medicinal chemistry[21] and catalysis.[22-25] However, their intrinsic air- and hydrolytic- sensitivities have hindered their broader applicability and are only considered as mere chemical curiosities. In spite of this, sporadic examples of robust cyclophosphazane frameworks have been reported.[26,27]

We and others have recently reported enhanced air- and hydrolytic-stability of cyclophosphazane frameworks by use of solution-based methods to oxidise their phosphorus centres with chalcogen elements.[26,27] Generally, the synthesis of such cyclophosph(V)azanes frameworks requires two steps; *(i)* nucleophilic substitution on the parent $[ClP(\mu\text{-}NR)]_2$ (**1**), followed by *(ii)* oxidation of the resulting phosph(III)azanes to phosph(V)azanes (Scheme 1).[27] Unfortunately, syntheses to date have involved multi-step reactions, generally requiring the isolation of intermediates and typically resulting in a mixture of cis/trans products that require further purification.[27] Typically these require prolonged reflux or reaction times (> 16 hr) for the quantitative conversion of each step. This combined with the large volumes of bulk solvents needed for their synthesis, purification and characterization, have rendered the mainstream synthesis of these species environmentally unsustainable.

Herein, we report the synthesis of highly robust disubstituted cyclophosph(V)azane-based compounds, by truncating a two-step reaction into a single orthogonal reaction (*i.e.*, substitution and oxidation in a one-pot one-step reaction) *via* mechanochemical ball milling (Scheme 1). Additionally, hydrolytic- and air-stability studies performed over a period of

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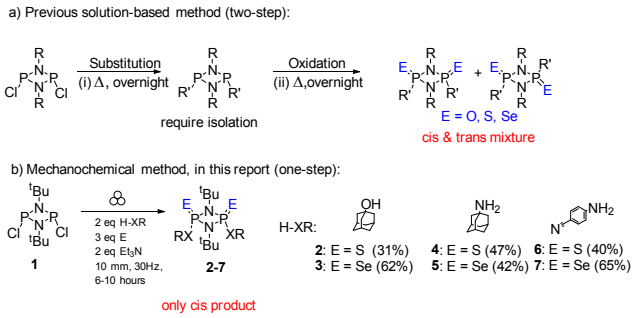

Scheme 1. a) General solution-based synthesis of phosph(V)azanes from dichlorocyclophosph(III)azanes.[27] b) Mechanochemical synthesis of compounds **2**-**7**. The symbol for mechanical milling has been proposed by Hanusa *et al.*[8]

1 month and 12 months, respectively, indicate that the compounds reported herein are highly air- and moisture-stable, and thus further expand the limited library of robust phosphazane frameworks known to date.

In the case of step (*i*), solution reactions of dichlorocyclophosphazane $[ClP(\mu\text{-}NR)]_2$ (**1**) with nucleophiles are commonly carried out in the presence of a Brønsted base (such as Et_3N) to produce air- and moisture-sensitive cyclodiphosph(III)azane derivatives.[28] The majority of the reported derivatives of **1** have been obtained through the use of alcohols or amines to generate symmetrically disubstituted products – the most prominent being the bis(amino)cyclodiphosphazane, $[(NH^tBu)P(\mu\text{-}N^tBu)]_2$. However, despite the plethora of examples of phosphazanes comprising bulky exocyclic substituents – and their successful applications as ligands in catalysis[22-25] – their repertoire is currently restricted to tert-butyl substituents. We therefore addressed the opportunity to synthesize and characterise new adamantyl species – which, in turn, may offer advantages over existing systems – and selected *para*-cyanoaniline to serve as a basis of comparison with reported *para*-cyanophenol derivatives.[17]

Initial reactions were conducted under inert atmosphere conditions by loading, **1** into a 10 mL stainless steel milling jar containing a 10 mm ball, an excess of elemental chalcogen (sulfur or selenium) and the appropriate organic acid (*i.e.*, alcohol or primary amine) in the presence of Et_3N in a 1:3:2:2 molar ratio. The mixture was then milled for a period ranging from 6 to 10 hours at 30 Hz (see Scheme 1b). The crude reaction mixture was isolated in a glove box before being purified by recrystallization (31-65 % isolated crystalline yield) and dried under vacuum for further characterization. All mechanochemical reactions produced the desired compounds in quantitative conversions, as indicated by $^{31}P\text{-}\{^1H\}$ nuclear magnetic resonance (NMR) spectra of their crude product forms (see ESI). More importantly, the solid-state reactions enabled exclusive formation of only one isomer, as indicated by the presence of a singlet resonance signal in the $^{31}P\text{-}\{^1H\}$ NMR spectra at δ 39.52, 24.62, 38.53, 23.45, 39.43, 30.09 ppm, for **2-7**, respectively (see ESI). Such stereoselective product formation is remarkable, as previously reported solution-based methods to obtain bis(amino)- and bis(alkoxy)-cyclophosph(V)azanes, typically results in a mixture of *cis/trans* isomers.[27,29] To compare our orthogonal mechanochemical approach with an analogous solution-based methods, a one-pot synthesis of **7** – as a test example - was attempted under overnight reflux in toluene. The reaction led to the formation of a mixture of products (see ESI) as shown by *in-situ* $^{31}P\text{-}\{^1H\}$ NMR spectroscopy; Illustrating, once more, the advantages that mechanochemistry often poses over solution method in main group synthesis.[1]

The ^1H spectra of **2-7** display resonance signals that are consistent with the presence of *tert*-butyl groups and either adamantanol, adamantylamine or *para*-cyanoaniline moieties for **2** and **3**, **4** and **5**, and **6** and **7**, respectively (see ESI). The infra-red (IR) absorption spectra for compounds **2-7** further corroborate the proposed structures; with compounds **4-7** exhibiting characteristic N-H stretching bands (3379, 3366, 3235 and 3287cm^{-1}, respectively). Moreover, stretching bands at 2220 and 2224 cm^{-1} indicative of nitrile groups are also observed for **6** and **7**. All spectroscopic data obtained (FTIR and NMR) is supportive of the successful mechanochemical synthesis of the desired products.

In addition to spectroscopic analyses, low temperature single-crystal X-ray diffraction (XRD) studies were also performed and are consistent with the initial proposed structures. Molecular structural determination from XRD data are in good agreement with our *in situ* $^{31}P\text{-}\{^1H\}$ NMR studies, where only the *cis*-oxidised isomer was observed. The *trans* products were not observed for compounds **2-5**, despite containing bulky adamantyl substituents,[12] an unusual finding given that one

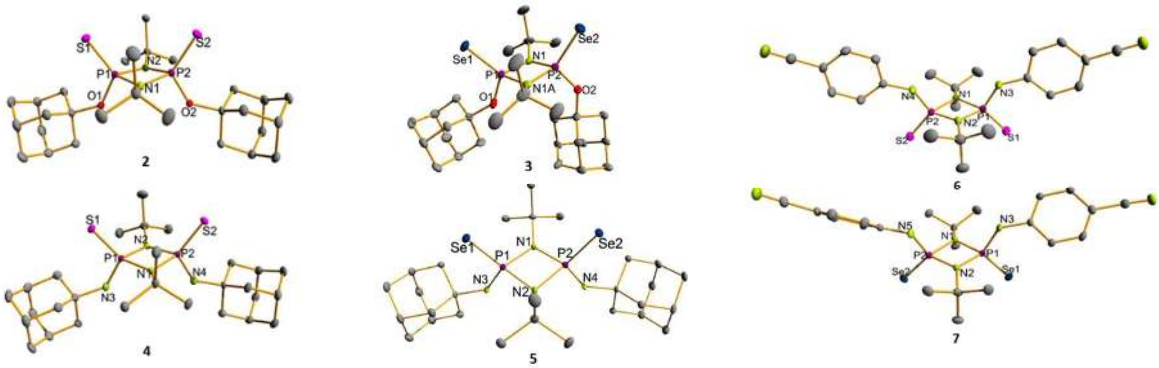

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Figure 1. Solid-state structures of compounds **2**-**7**. Hydrogen atoms and/or solvate molecules are omitted for clarity.

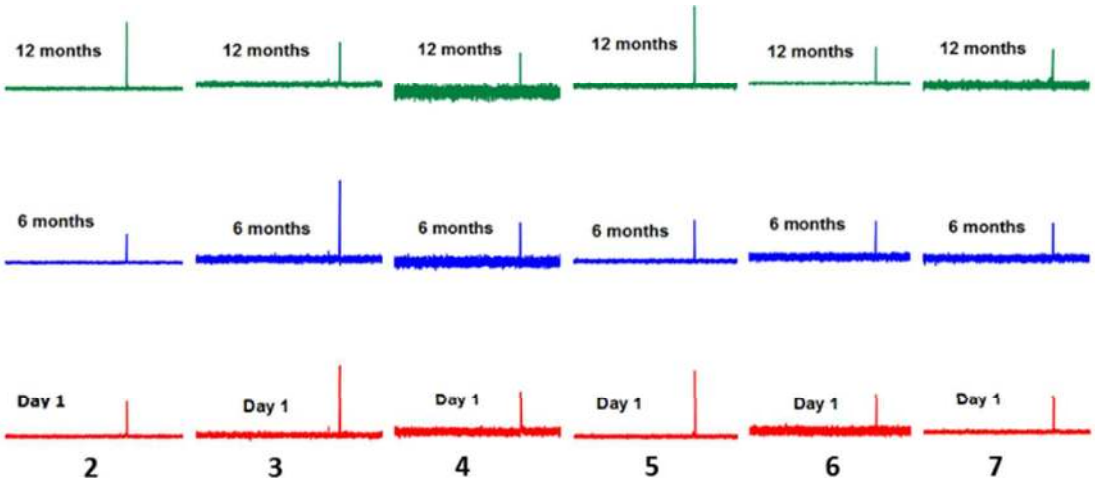

Figure 2. ^{31}P-{^{1}H} NMR spectrum of compounds **2**-**7** after exposure to air for 1 day (bottom), and 3 (middle) and 6 months (top), respectively (in THF).

would normally expect that steric repulsion would favour the formation of the *trans* product.

The crystal structures of compounds **2-7** are also unique. These compounds crystallized in monoclinic, orthorhombic and triclinic crystal systems for **2**-**3** and **5, 4** and **7**, and **6**, respectively. The P_2N_2 endocyclic P-N bond distances for all compounds falls within the range of 1.68 -1.70 Å, consistent with previously reported related compounds [(NH^{t}Bu)(E)P(μ-N^{t}Bu)]$_2$[29] and [(*p*-OC$_6$H$_4$CN)(E)P(μ-N^{t}Bu)]$_2$[27] where E = S, Se (1.68 - 1.70 Å and 1.67 - 1.69 Å, respectively). Moreover, the mean exocyclic P-O and P-N distances in compounds **2** and **3**, and **4**-**7** (1.57 and 1.58 Å and 1.63, 1.64, 1.65 and 1.66 Å, respectively) are also found to be within the expected ranges for these compounds.[29,30] All three pairs of compounds, namely **2/3**, **4/5**, and **6/7**, despite their structural similarities, displayed subtle differences in their molecular solid-state structures. All compounds were observed to adopt an exo, exo orientation with the exception compound **3**, which exists as an exo, endo orientation (Figure 1). In set **4**/**5**, compound **4** crystallizes as a tetrahydrofuran (THF) solvate, where the THF molecule undergoes intermolecular hydrogen bonding with the exocylic NH group. It is noteworthy that in the last pair consisting of **6**/**7**, **6** cocrystalizes with one molecule of triethylammonium chloride and one molecule of THF. The chloride anion forms bifurcated hydrogen bonds with the two exocyclic N-H protons, as well as charge-assisted hydrogen bonds with the triethylammonium cation (see ESI). Such anion-hydrogen bond motif is analogous to [(NHAr)(O)P(μ-N^{t}Bu)]$_2$ (where Ar = Ph, *m*-(CF$_3$)$_2$Ph) as described by Goldfuss *et al.*, in which the authors report that these cyclophosphazane species represent versatile building blocks for anion recognition,[31] further highlighting the potential applicability for these cyclophosphazane frameworks. On the other hand, compound **7**, crystallized as a methanol solvate. The crystal structure of **7** is unique, in that the cyclophosphazane is able to self-assemble by forming intermolecular hydrogen bonds between the exocyclic N-H protons, the methanol molecules and the nitrile substituents on the aromatic rings of adjacent molecules, creating a one-dimensional supramolecular corrugated catemer. (see ESI). To the best of our knowledge, the only other account of a similar supramolecular polymeric motif was reported by Balakrishna *et al.*, in which *trans* phosphazane building blocks are bridged by water molecules, creating linear hydrogen-bonded chains.[32]

Employing ^{31}P-{^{1}H} NMR to monitor the air-stability of **2**-**7** as samples stored "on the bench", we confirmed that all compounds are highly robust, failing to show any signs of decomposition, even at the 12-month time-point (Figure 2). Hydrolytic stability tests were performed using a previously established methodology.[27] To improve and standardize our results across the series of compounds **2**-**7**, their solubility was assessed across a range of solvent systems (see ESI). On determination that the optimal solvent system comprised THF:water in a 5:1 ratio, appropriate samples of **2**-**7** were prepared and their ^{31}P-{^{1}H} NMR spectra recorded over a period of one month. With the exception of **5**, all compounds were resistant to hydrolysis, even after 28 days (see ESI). This is consistent with previously reported water-stable phosphazane systems, enabling compounds **2**-**7** to be considered as new additions to the small family of air and water-stable cyclophosphazanes.

In summary, we have demonstrated the orthogonal "one-step one-pot" synthesis of a series of cyclophosph(V)azane frameworks *via* ball milling. Some of these cyclophos-ph(V)azanes bear sterically bulky adamantyl groups, yet adopt a *cis*- conformation when synthesized, as confirmed by XRD and NMR analysis. Stability studies conducted have also shown that these compounds are bench-top stable, without showing signs of decomposition, even after 12 months.

The novel use of orthogonality as a design strategy in the functionalization of main group compounds, in which two mutually exclusive reactions can be truncated into a single

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step, serves to demonstrate how orthogonality and mechano-chemistry are compatible with each other, and can be employed within the main group chemistry arena. We hope the herein presented work triggers additional efforts towards the development of greener methods in main group chemistry.

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